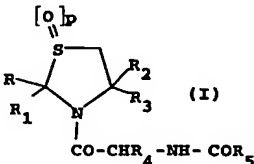
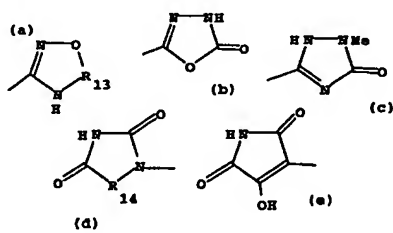


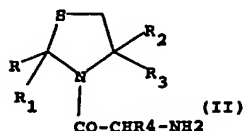
<p>94-242602/30 B03 RHON 93.01.07 RHONE-POULENC RORER SA 93.01.07 93FR-000076 (94.07.08) C07D 277/04, A61K 31/425, C07D 277/10 New thiazolidine derivs. with affinity for cholecystokinin and gastrin receptors - are used to treat e.g. psychosis, anxiety, irritable colon syndrome, tumours and pancreatitis. C94-110770 Addnl. Data: DUBROEUCQ M, MANFRE F</p>	<p>B(7-F1, 14-J2C) .2</p>
<p>Thiazolidine derivs. of formula (I) and their salts and isomers are new:</p>  <p style="text-align: center;">(I)</p>	<p>R = 1-12C alkyl, 3-12C cycloalkyl or 6-12C polycycloalkyl (all opt. mono or polyunsatd); phenylalkyl, (opt. ring-substd. by alkyl, alkoxy and/or halo); diphenylalkyl; cinnamyl; pyridyl, furyl, thienyl, quinolyl, naphthyl or indolyl (all opt. substd. by one or more alkyl); or phenyl (opt. substd. by halo, alkyl, alkoxy, OH, NO₂, amino, mono- or di-alkylamino, alkoxy-carbonyl, CONR₇R₈, NHCOMe, CF₃, Ph and/or OCF₃); oxo-2-piperidyl; or quinuclidinyl; R₁, R₃ = H, alkyl, cycloalkyl, phenylalkyl or phenyl (opt. substd. by halo, alkyl and/or alkoxy); R₂ = (CH₂)_n-COR₆, (CH₂)_mOCOR₆, -(CH₂)_mNR₉R₁₀ or oxazoliny (opt. substd. by alkyl, and/or alkyl-3-oxadiazolyl); R₄ = H or alkyl; R₅ = phenyl (opt. substd. by halo, alkyl, alkoxy, and/or alkylthio), naphthyl, indolyl, quinolyl, or phenylamino (opt. ring substd. by halo, alkyl, alkoxy, alkylthio, CF₃, COOH, alkoxy-carbonyl, OH, NO₂, amino, acyl, CN, sulphonamoyl, carbamoyl, hydroxyimino alkyl, alkoxyiminoalkyl, hydroxyamino carbonyl,</p> <p style="text-align: right;">FR 2700168-A+</p>

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<p>alkoxyaminocarbonyl, tetrazol-5-yl, tetrazol-5-ylalkyl, trifluoromethylsulphonamido, alkylsulphinyl, mono- or polyhydroxyalkyl, sulpho, alk-O-CO-alk, alk-COOX, alk-O-alk, alk¹-COOX, O-alk-COOX, CH=CHCOOX, COCO₂X, alkSO₃H (or its salt), CH=CH-alk¹, C(=NOH)CO₂X, S-alk-CO₂X, SO-alk-CO₂X, SO₂-alk-CO₂X, OCH₂alk¹-COOX, CX=N-O-alk-CO₂X, alk-N(OH)-CO-alk, alkSO₃H, SO₂NHCO₂R₁₁, SO₂NHSO₂R₁₁, CONHCO₂R₁₁, CONHSO₂R₁₁, B(OH)₂, C(NH₂)=NOH, SO₂NHR₁₂, CONHR₁₂, 2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl or a gp. of formula (a)-(e);</p>  <p style="text-align: center;">(a) (b) (c) (d) (e)</p>	<p>R₆ = OH, alkoxy, cycloalkoxy, cycloalkyl-alkoxy, phenyl or NR₉R₁₀; R₆ = alkoxy, cycloalkoxy, cycloalkylalkoxy, phenyl or NR₉R₁₀; R₇ = H, alkyl, phenyl alkyl or phenyl (opt. substd. by halo, alkyl, alkoxy and/or alkylthio); R₈ = alkyl, phenylalkyl or phenyl (opt. substd. by halo, alkyl, alkoxy and/or alkylthio); or NR₇R₈ = mono- or polycyclic opt. unsatd. heterocycle contg. 4-9C atoms and 1 or more O or N atoms and opt. substd. by one or more alkyl; R₉ = H, alkyl, cycloalkylalkyl, cycloalkyl, phenylalkyl or phenyl (opt. substd. by halo, alkyl, alkoxy, and/or alkylthio); R₁₀ = alkyl, cycloalkyl, cycloalkylalkyl; phenylalkyl, or phenyl (opt. substd. by halo, alkyl, alkoxy and/or alkylthio); or NR₉R₁₀ = mono- or polycyclic opt. unsatd. heterocycle contg. 4-9C and 1 or more O, N and S, and opt. substd. by one or more alkyl; R₁₁ = alkyl, cycloalkyl, CF₃ or phenyl (opt. substd. by CN, alkoxy, NO₂, amino and/or halo); R₁₂ = tetrazol-5-yl; R₁₃ = CO or SO; R₁₄ = O or CO; n, p = 0-2;</p> <p style="text-align: right;">FR 2700168-A+/1</p>
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<p>94-242602/30</p> <p>m = 1 or 2; X = H, alkyl, or phenyl alkyl; alk = alkyl or alkylene; and alk¹ = hydroxyalkyl, hydroxyalkylene, alkoxyalkyl or alkoxyalkylene; unless otherwise stated all alkyl moieties contain 1-4C; acyl moieties contain 2-4C and cycloalkyl moieties contain 3-6C; provided that : n is not 0 when R, R₃ = H and R₁ = pyridyl, furyl, thienyl, quinolyl, naphthyl or indolyl (all opt. substd. by one or more alkyl) or phenyl (opt. substd. by halo, alkyl, alkoxy, OH, NO₂, amino, mono- or di-alkylamino, alkoxy-carbonyl, CONR₇R₈, NHCOMe, CF₃ or OCF₃).</p> <p>USE</p> <p>(I) have strong affinity for cholecystokinin (CCK) and gastrin receptors. They are particularly useful in the treatment and prevention of disorders due to CCK and gastrin in the nervous system and GI tract. They are used to treat and prevent psychoses, anxiety, depression, neurodegeneration, panic attacks, Parkinson's disease, tardive dyskinesia, irritable bowel syndrome, pancreatitis, ulcers, intestinal motility disorders, certain tumours sensitive to CCK, memory dysfunction, chronic withdrawal and abuse of alcohol or</p>	<p>drugs, as pupil constrictors, analgesics or as potentiators for analgesics (both narcotic and non narcotic), and as appetite regulators.</p> <p>DOSAGE</p> <p>Dosage is pref. oral at 0.05-1g/day in unit doses of 10-500 mg.</p> <p>ADVANTAGE</p> <p>(I) have low toxicity e.g. LD₅₀ of more than 40 mg/kg in mice.</p> <p>PREPARATION</p> <p>4 methods are claimed e.g. as follows: (I; p = 0, R₅=R₅¹) is prep'd. by reacting a carbamic acid deriv. obtd. opt. in situ by reaction of a carbonic acid deriv. chosen from N,N'-diimidazolecarbonyl, phosgene, triphosgene and p-nitrophenyl-chloroformate with a thiazole cpd. of formula (II), and with an aniline deriv. where the phenyl ring is opt. substd. by Q, and opt. salifying.</p> <p style="text-align: right;">FR 2700168-A+/2</p>
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R₃¹ = phenylamino (opt. ring subst.);
 Q = halo, alkyl, alkoxy, alkylthio, CF₃, COOH, alkoxycarbonyl, OH,
 NO₂, amino, acyl, CN, sulphonamoyl, carbamoyl,
 hydroxyiminoalkyl, alkoxyiminoalkyl, hydroxyaminocarbonyl,
 alkoxyaminocarbonyl, tetrazol-5-yl, tetrazol-5-ylalkyl,
 trifluoromethylsulphonamido, alkylsulphinyl, mono- or
 polyhydroxyalkyl, sulfo, alk OCOalk, alkCOOX, alkO-alk,
 alk¹-COOX, O-alkCOOX, CH=CHXCOOX, COCO₂X,
 alkSO₃H, CH=CH-alk¹, C(=NOH)-CO₂X, S-alkCO₂X,
 SOalkCO₂X, SO₂alkCO₂X, OCH₂alk¹CO₂X, CX=NO-alk-CO₂X,

alk-N(OH)-CO-alk, 2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl,
 alkSO₂H, SO₂NHCOR₁₁, SO₂NHSO₂R₁₁, CONHCOR₁₁,
 CONHSO₂R₁₁, B(OH)₂, C(NH₂)=NOH, SO₂NHR₁₂, CONHR₁₂
 or a gp. (a)-(e).

Cpds. (I) may be interconverted.

EXAMPLE

A soln. of 1.38g (4R)-tertbutyl 3-(2-aminoacetyl)
 2-cyclohexyl 4-thiazolidine carboxylate in 25ml CHCl₃ was treated at
 25°C with 1.1g benzyl 3-isocyanatophenylacetate in 10ml CHCl₃. The
 mixt was stirred for 12hrs at 25°C, conc., and worked up to give 2.1g
 benzyl (4R)-3-(3-(2-(4-tertbutoxy carbonyl-2-cyclohexyl
 3-thiazolidinyl) 2-oxo-ethyl) ureido) phenylacetate. 2g this prod., 1.7g
 ammonium formate and 2g 10% Pd/C were treated with 30cm³ MeOH
 slowly under inert atmos. The mixt was refluxed for 2hrs and cooled
 to 25°C. The catalyst was filtered off and the filtrate was conc. and
 dried under reduced pressure at 40°C. The residue was dissolved in
 25cm³ aq 1N NaOH, and washed with Et₂O (2x10ml). The aq phase
 was adjusted to pH2 by addn of aq. 1N H₂SO₄. The ppt was filtered,
 washed and air dried to give 1g of (4R)-3(3(2-4-tertbutoxy carbonyl
 2-cyclohexyl 3-thiazolidinyl) 2-oxoethyl-ureido) phenylacetic acid

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m.pt. 115°C.

In tests (I) have IC₅₀ value of < 1000nM for inhibition of
 binding to CCK receptors. (59pp1858DwgNo.0/0)

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